REMARKS

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-128, and 142-198 were pending in this application before entry of the amendments made herein. Claims 169-178 and 192-198 have been withdrawn by the Examiner as being drawn to non-elected inventions.

As a preliminary matter, Applicant points out that, while the Office Action Summary lists claims 91, 92, 96, 98, and 124 as rejected, these claims are not rejected in the Office Action itself on pages 2-8.

Applicant has amended claims 62, 63, 65, 68, 69, 92, 98, 112, 119, 121, 124-128, 142-150, 155-159, 164-183, 188, 192-198 to clarify the claimed invention. In particular, claims 62, 63, 65, 68, 69, 92, 98, 112, 119, 121, 124-128, 142-150, 155-159, 164-183, 188, and 192-198 have been amended to recite an isolated HIV Tat protein, fragment or mutant, a wildtype HIV Tat protein, a HIV Tat mutant, and/or a HIV Tat fragment. Support for the amendments can be found in the specification at, *inter alia*, page 1, lines 4-6; page 14, lines 21-23; and page 17, lines 9-14.

Claims 62, 125, 126, 171, 176, 179, 192, 193, and 196 have been amended to correct the sequence identifiers for the amino acid sequences of the recited mutants. In particular, the sequence identifier for the amino acid sequence of the Cys22 mutant is SEQ ID NO:4; the sequence identifier for the amino acid sequence of the Lys41 mutant is SEQ ID NO:6; and the sequence identifier for the amino acid sequence of the RGDΔ mutant is SEQ ID NO:8. On November 5, 2002, Applicant submitted a new computer readable form (CRF) and a hard copy of the sequence listing and amended the specification to indicate that the sequence identifiers for the amino acid sequences of the Cys22, Lys41, and RGDΔ mutants are SEQ ID NOS:4, 6, and 8, respectively.

In addition, claim 179 has been amended such that the recitation that the isolated HIV Tat protein, fragment or mutant "comprises the cysteine rich region of Tat" has been deleted, since the mutant having the amino acid sequence of SEQ ID NO:4 and the fragment having the amino acid sequence of SEQ ID NO: 16 or 17 do not contain the cysteine rich region of HIV Tat.

No new matter has been added. Upon entry of the present amendments, claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-128, and 142-198 will be pending in the present application.

I. THE CLAIM OBJECTIONS

Claims 62, 125 and 126 are objected to because the claim limitation "amino acid sequence" does not match SEQ ID NO:7 and SEQ ID NO:9, which are nucleotide sequences. In response, Applicant has amended the objected to claims, as well as claims 171, 176, 179, 192, 193, and 196, to correct the sequence identifier of the recited mutants. In particular, the recitation "SEQ ID NO:7, 8 or 9" in claims 62, 125, 179, 193, and 196 has been replaced with "SEQ ID NO:4, 6 or 8." The recitation "SEQ ID NO:7" in claims 126, 171, 176, and 192 has been replaced with "SEQ ID NO:4." Applicant submits that the mutants recited in claims 62, 125, 179, 193, and 196 refer to the Cys22, Lys41, and RGDΔ mutants, and the mutant recited in claims 126, 171, 176, and 192 refers to the Cys22 mutant. Through inadvertent error, Applicant incorrectly identified the sequence identifiers for the amino acid sequences of these mutants. In view of the sequence listing submitted and the amendments to the specification made in the Response to Office Action of August 7, 2002 filed November 5, 2002, Applicant submits that the sequence identifiers for the amino acid sequences of the Cys22, Lys41, and RGDΔ mutants are SEQ ID NOS:4, 6 and 8, respectively. Thus, the recitation "amino acid sequence" in amended claims 62, 125 and 126 matches SEQ ID NO:4, SEQ ID NO:6, and SEQ ID NO:8. As such, the objection is believed to be obviated and should be withdrawn.

II. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

The Examiner has maintained the rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, and 186 under 35 U.S.C. § 102(b) ("Section 102(b)") as allegedly being anticipated by Chang *et al.* (AIDS, 1997 Oct; 11(12):1421-1431). Specifically, the Examiner alleges that although Applicant argues that Chang *et al.* is silent as to whether the resulting Tat composition is pharmaceutically acceptable for administration to a human, "the 'wherein' clause reciting 'pharmaceutically acceptable for administration to a human' is not given patentable weight because the intended use does not materially limit the claimed composition to a particular structure that distinguishes over the prior art Tat protein composition" (see Office Action, page 5, ¶3, lines 3-6). Inconsistent with the foregoing statement, the Examiner adds that "[e]ven the Applicant herself admits that the claim limitation is an attribute or characteristic of the claimed composition, and is not a use limitation" and quotes Applicant's remarks on

page 16 of the Amendment Under 37 C.F.R. § 1.114 filed October 22, 2007[1] (see Office Action, page 5, ¶3, lines 6-8). For the following reasons, Applicant disagrees.

Applicant respectfully points out that the Examiner is incorrect in stating that the wherein clause is merely an intended use that does not materially limit the claimed composition. Quite to the contrary, the "wherein" clause states a feature that materially limits the components of the composition. In particular, as discussed at length in the Amendment Under 37 C.F.R. § 1.114 filed June 14, 2006 (see pages 16-18), the phrase "pharmaceutically acceptable for administration to a human" in claims 62, 172, 192, 193 and 196 means that the composition is sufficiently safe for administration to human patients using the criteria for safety defined by regulatory agencies such as the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA), *i.e.*, it does not contain ingredients that the skilled artisan would know, based on knowledge common in the art, would result in denial of regulatory approval for marketing as a drug for humans. The recitation imposes a structural limitation to the claimed composition in that it cannot contain ingredients (*e.g.*, unsafe substances such as phenylmethylsulfonyl fluoride (PMSF), acetonitrile, trifluoroacetic acid (TFA), etc.) that would result in denial of regulatory approval for marketing as a drug for humans. Accordingly, the recitation requires the avoidance of such ingredients, and neither suggests nor makes optional the inclusion of such ingredients. Thus, the recitation must be given patentable weight in the determination of the scope of the claim.

The Examiner relies on MPEP § 2111.04 and case law regarding a "whereby" clause to support the claim rejection. Neither the MPEP nor the cited case law supports the Examiner's position. Section 2111.04 of the MPEP states that certain clauses, including the "wherein" clause, "may raise a question as to the limiting effect of the language in a claim," and that "[t]he determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case." MPEP, 8th Ed, Rev. Sept. 2007 at page 2100-46,

The case law cited by the Examiner is *Hoffer v. Microsoft Corp.* (citing *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003)), 405 F.3d 1326, 1329, 74 U.S.P.Q.2d 1481, 1483 (Fed. Cir. 2005)). The court in *Hoffer v. Microsoft Corp.* stated that "[i]t is correct that a 'whereby' clause generally states the result of the patented

[1] The U.S. Patent and Trademark Office incorrectly accorded a filing date of October 24, 2007 to the Amendment, even though said Amendment was filed by "Express Mail Post Office to Addressee" service of the United States Postal Service pursuant to 37 C.F.R. § 1.10 on October 22, 2007.

process. However, when the 'whereby' clause states a condition that is material to its patentability, it cannot be ignored in order to change the substance of the invention" (emphasis added). In *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, the court stated that "[a] whereby clause in a *method* claim is not given weight when it simply expresses the intended result of a *process step* positively recited," 336 F.3d at 1381 (emphasis added). None of the pending claims are directed to a method reciting a process step with a "whereby" clause that simply expresses the result of a process. Firstly, the rejected claims are not directed to a process; secondly, the "wherein" clause is material to the patentability of the claimed composition. Thus, to the extent the case law cited by the Examiner is applicable to a "wherein" clause in a composition claim, *i.e.*, the recitation in claims 62 and 179, it supports Applicant's position that the "wherein" clause limits the structure of the claimed composition as discussed above. Accordingly, Applicant submits that the Examiner's construction of the "wherein" clause is incorrect.

The Examiner is correct that Applicant stated on page 16 of the Amendment Under 37 C.F.R. § 1.114 filed October 22, 2007 that something that is "pharmaceutically acceptable for administration to a human" is not a use limitation. Applicant's statement does not mean that the recitation "pharmaceutically acceptable for administration to a human" is not a claim limitation. As discussed above, the recitation describes the composition itself as acceptable for a particular use, thereby limiting the contents of the composition. While the claimed composition must be pharmaceutically acceptable for administration to a human, it need not be used for administration to a human, and thus the recitation limits the content but not the use of the composition.

The relevant case law regarding anticipation was discussed in Applicant's Amendment filed May 1, 2007 (see pages 12-14), and is not repeated herein. As previously discussed in the Amendment Under 37 C.F.R. § 1.114 filed October 22, 2007 (see pages 20-22), the purification methods disclosed by Chang *et al.* fail to explicitly and inherently disclose a Tat composition that is pharmaceutically acceptable for administration to a human, and thus, cannot anticipate the claimed subject matter.

Regarding the first purification method of Chang *et al.*, (as that method is referred to in the Response Under 37 C.F.R. § 1.111 with Amendments filed December 13, 2005), Chang *et al.* is silent as to whether the resulting Tat composition is pharmaceutically acceptable for administration to a human, and thus, does not *explicitly* anticipate the claimed composition. Since the resulting Tat composition *may*, and did in fact, include acetonitrile

and TFA from the HPLC step (see ¶6 of the Declaration of Barbara Ensoli, M.D., Ph.D. Under 37 C.F.R. § 1.132 filed December 13, 2005), the first purification method of Chang *et al.* would not *necessarily*, *inevitably*, and *always* be pharmaceutically acceptable for administration to a human, and thus, does not *inherently* anticipate the claimed composition. *See In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

Regarding the second purification method of Chang *et al.*, (as that method is referred to in the Response Under 37 C.F.R. § 1.111 with Amendments filed December 13, 2005), Chang *et al.* explicitly states that PMSF is included in the resulting Tat composition. The inclusion of PMSF renders the composition unsuitable for regulatory approval for human administration (see ¶7 of the Second Declaration of Shayne Gad, Ph.D. Under 37 C.F.R. § 1.132 filed June 14, 2006), *i.e.*, not pharmaceutically acceptable for administration to a human. Clearly, the fact that the Tat composition contains PMSF means that the second purification method of Chang *et al.* does *not* inherently teach a Tat composition that is pharmaceutically acceptable for administration to a human.

For the foregoing reasons, the Tat compositions obtained by the purification methods disclosed by Chang *et al.* are neither explicitly nor inherently disclosed by Chang *et al.* to be pharmaceutically acceptable for administration to a human, as recited in claims 62 and 179. Therefore, Chang *et al.* does not teach each and every element of claims 62 and 179, and thus, their respective dependent claims. Withdrawal of the Section 102(b) rejections is respectfully requested.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 114, 119, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, 186 and 189 are rejected under 35 U.S.C. § 103(a) ("Section 103(a)") as allegedly being obvious over Chang *et al.* (AIDS, 1997 Oct; 11(12):1421-31) in view of Heiman (web pages entitled "HIV Vaccines: Where are we Going?" http://www.niaid.nih.gov/daids/vaccine/1998nature.htm). Claims 62, 63, 65, 66, 68, 69, 89, 90, 93-95, 97, 101-103, 105-111, 116, 117, 121, 122, 128, 142-168, 179-187, 190, and 191 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* in view of Vogel *et al.* ("A compendium of vaccine adjuvants and excipients." In: Powell MF, Newman MJ, editors. Vaccine design: The Subunit and Adjuvant Approach. Plenum, New York, 1995). Claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 99, 106, 107, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, and 186 are rejected under 35 U.S.C. §

103(a) as allegedly being obvious over Chang *et al.* in view of Castignolles *et al.* (Vaccine, 1996 Oct; 14(14):1353-60). Claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 100, 106, 107, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, and 186 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* in view of Ramshaw *et al.* (J Immunol Methods, 1977; 18(3-4):251-5). Claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 112, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, 186, and 188 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* in view of Livingston *et al.* (J Immunol., 1997 Aug 1; 159(3):1383-92). Claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 123, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, and 186 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* in view of Barry *et al.* (Clin Pharmacokinet., 1997 Mar; 32(3):194-209). For the following reasons, Applicant disagrees.

1. The Legal Standard

In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467; *see also* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* ("Examination Guidelines"), Federal Register, Vol. 72, No. 195, October 10, 2007, pages 57527-57528. The Supreme Court also stated that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...." *KSR*, 127 S.Ct. at 1741, 82 U.S.P.Q.2d at 1396.

In *Graham*, the Supreme Court explained that secondary considerations such as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized in determining the obviousness or nonobviousness of the invention. 383 U.S. at 17-18, 14 U.S.P.Q. at 467. Following *Graham*, the Court of Customs and Patent Appeals (CCPA) and its present successor, the Court of Appeals for the Federal Circuit (CAFC), have held the following considerations to be objective evidence of nonobviousness: long felt need,

commercial success, failure of others, copying and unexpected results. *See, e.g., Avia Group Int'l Inc. v. L.A. Gear California, Inc.*, 853 F.2d 1557, 7 U.S.P.Q.2d 1548 (Fed. Cir. 1988); *In re Sernaker*, 702 F.2d 989, 217 U.S.P.Q. 1 (Fed. Cir. 1983). Evidence that experts expressed skepticism upon learning of the invention is also probative evidence of nonobviousness. *See, e.g., United States v. Adams*, 383 U.S. 39, 52 (1966); *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 697-698, 218 U.S.P.Q. 865, 869 (Fed. Cir. 1983) ("Expressions of disbelief by experts constitute strong evidence of nonobviousness."); *Burlington Industries Inc. v. Quigg*, 822 F.2d 1581, 3 U.S.P.Q.2d 1436 (Fed. Cir. 1987) (testimony that the invention met with initial incredulity and skepticism of experts was sufficient to rebut the *prima facie* case of obviousness based on the prior art); *In re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988) ("The skepticism of an expert, expressed before these inventors proved him wrong, is entitled to fair evidentiary weight....").

The CAFC has consistently made clear that when evidence of such secondary considerations is present, it must be considered by the Examiner or a court in determining a question of obviousness. *See e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983). "Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence...." *Stratoflex Inc. v. Aeroquip*, 713 F.2d at 1538-39, 218 U.S.P.Q. at 879. Such secondary considerations provide evidence that can both rebut a *prima facie* case of obviousness and demonstrate the nonobviousness of the claimed invention. *See e.g., In re Piasecki*, 745 F.2d 1468, 223 U.S.P.Q. 785 (Fed. Cir. 1984).

2. The Examiner's Characterization of the Two Magnani Declarations is Incorrect

As a preliminary matter, Applicant submits that the Examiner has mischaracterized the evidence and statements which were made in the Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 ("First Magnani Declaration") filed May 1, 2007 and the Supplemental Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 filed October 22, 2007. In the Office Action, the Examiner alleges that "[e]ven though there is no explicit

suggestion to avoid the use of PMSF in the Chang reference, applicant has admitted on the record that it is commonly known in the art as of December 1st, 1997...to avoid the use of PMSF in the process in routine experimentation, as evidenced by the two Magnani declarations" (see Office Action, paragraph bridging pages 6 and 7). Applicant disagrees for the following reasons:

Contrary to the Examiner's allegation, the two Magnani declarations do not show that it was commonly known in the art to routinely avoid the use of PMSF. Rather, the two Magnani declarations show that a person skilled in the art as of December 1, 1997, based on the teaching of the specification and knowledge common in the art as of December 1, 1997, and using only routine experimentation, would be able to use common knowledge in the art to obtain a composition that was pharmaceutically acceptable for administration to a human, *e.g.*, that lacked PMSF, without undue experimentation (once knowledge of the instant specification had motivated him/her to do so). While the two Magnani declarations show that such a person *could* avoid the use of PMSF, the declarations do not show that it was routine to do so. Neither one of the Magnani declarations states or suggests that the person skilled in the art as of December 1, 1997 would have reason to modify the known procedures for obtaining a biologically active Tat, which result in a composition that is not pharmaceutically acceptable for administration to humans (see, *e.g.*, Chang *et al.*), to obtain a biologically active Tat in a composition that would be pharmaceutically acceptable for administration to a human. In fact, for reasons discussed below, Applicant submits that the person skilled in the art as of December 1, 1997 would *not* have reason to modify the known procedures for obtaining a biologically active Tat (including the procedures disclosed in Chang *et al.*) to obtain a biologically active Tat in a composition that would be pharmaceutically acceptable for administration to a human.

3. The Claimed Invention Presents Secondary Considerations That Are Objective Evidence Of Nonobviousness

First, Applicant submits that there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with in any of the other references cited in support of the Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that PMSF and other components that are not pharmaceutically acceptable for administration to a human are avoided. More importantly, there is no common sense or any reason that would have prompted a person of ordinary skill in the relevant field to modify the

purification methods of Chang *et al.*, which result in compositions that are not pharmaceutically acceptable for administration to a human, to obtain a biologically active HIV Tat (or biologically active HIV Tat mutant or fragment) in a composition that would be pharmaceutically acceptable for administration to a human, because of the concern in the art that biologically active HIV Tat (or a biologically active HIV Tat mutant or fragment) would be harmful when administered to humans.

The Examiner's attention is respectfully directed to a Third Declaration of Barbara Ensoli, M.D., Ph.D. Under 37 C.F.R. § 1.132 with Exhibits 1-43 ("Third Ensoli Declaration"), submitted concurrently herewith as objective evidence of nonobviousness. Applicant submits that, when applying the proper standard for determining obviousness, and in view of the secondary considerations evidenced by means of the Third Ensoli Declaration, the cited references do not render the claimed invention obvious.

One of ordinary skill in the art as of December 1, 1997 would not have reason to modify the known procedures for obtaining a biologically active HIV Tat, which result in a composition that is not pharmaceutically acceptable for administration to humans, to obtain a biologically active HIV Tat (or biologically active HIV Tat mutant or fragment) in a composition that would be pharmaceutically acceptable for administration to a human, because it was commonly known that biologically active HIV Tat (or a biologically active HIV Tat mutant or fragment) had many activities that were believed to result in harmful health effects (see Third Ensoli Declaration, ¶¶3-12). In particular, as of December 1, 1997, it was well known to one of ordinary skill in the art that biologically active HIV Tat plays an essential role in HIV replication and viral gene expression and contributes to the pathogenesis of HIV, and thus, that the administration of biologically active HIV Tat to humans would be undesirable (see Third Ensoli Declaration, ¶4); (ii) induces immune hyperactivation, which was speculated to be critical for the maintenance of the HIV infectious process and was thought possibly to contribute to development of cancer in AIDS (see Third Ensoli Declaration, ¶5); (iii) protects HIV-infected T cells from apoptosis (leading to disease progression) but induces apoptosis in uninfected T cells (leading to severe immune suppression) (see Third Ensoli Declaration, ¶6); (iv) protects uninfected T cells from apoptosis, perhaps contributing to cancer development in HIV-infected individuals (see Third Ensoli Declaration, ¶7); (v) has immunosuppressive effects (see Third Ensoli Declaration, ¶8); (vi) increases production of a number of inflammatory cytokines that adversely affect the functions of uninfected cells, which had been suggested as contributing to the pathogenesis of

AIDS and AIDS-associated disorders (see Third Ensoli Declaration, ¶9); (vii) causes damage to vital organs such as the central nervous system (see Third Ensoli Declaration, ¶10); (ix) acts as an exogenous growth factor that promotes the growth of AIDS-Kaposi's sarcoma cells (see Third Ensoli Declaration, ¶11); and (x) enhances the chemotactic and invasive behaviors of monocytes, possibly recruiting monocytes into extravascular tissues, a process which was speculated to contribute to the destruction of tissues and cellular architecture seen in patients with AIDS (see Third Ensoli Declaration, ¶12). The publications discussed in Paragraph Nos. 3-12 of the Third Ensoli Declaration are evidence of prejudice in the prior art against the formulation of a biologically active HIV Tat (or biologically active HIV Tat mutant or fragment) in a composition that would be pharmaceutically acceptable for administration to a human, and thus evidence the lack of reason in the prior art to modify the purification methods of Chang *et al.* to include a biologically active HIV Tat (or biologically active HIV Tat mutant or fragment) in a composition that would be pharmaceutically acceptable for administration to a human. The knowledge in the art that biologically active HIV Tat (or a biologically active HIV Tat mutant or fragment) had many activities that were believed to result in harmful health effects made it unexpected that a composition comprising biologically active HIV Tat (or a biologically active HIV Tat mutant or fragment) would be beneficial and safe when administered to humans (see Third Ensoli Declaration, ¶17). Contrary to the prejudice in the art, results of a human clinical trial using a biologically active Tat showed that the biologically active Tat was safe and well tolerated in all subjects in the trial (see Paragraph Nos. 6-10 of Second Declaration of Barbara Ensoli, M.D., Ph.D. Under 37 C.F.R. § 1.132 filed May 1, 2007).

Furthermore, Applicant submits that even after the claimed invention was disclosed, there was clear skepticism and disbelief as to the safety of administering biologically active HIV Tat (or a biologically active HIV Tat mutant or fragment) to humans, showing the continuing prejudice in the art against the administration of biologically active HIV Tat (or a biologically active HIV Tat mutant or fragment) to humans, and thus the continuing disincentive to change standard purification procedures for biologically active HIV Tat so as to formulate it in a composition pharmaceutically acceptable for administration to humans (see Third Ensoli Declaration, ¶13). In particular, when the inventor Dr. Barbara Ensoli reported during a meeting that the administration of a biologically active HIV Tat to monkeys was safe and effective in eliciting an immune response, and announced future testing of biologically active HIV Tat in humans, a number of experts in the field of AIDS expressed

concern regarding the use of biologically active HIV Tat, stating that use of biologically active HIV Tat could be dangerous (see Third Ensoli Declaration, ¶14). A former coworker of the inventor, Dr. Robert Gallo, also warned against the use of biologically active HIV Tat in humans (see Third Ensoli Declaration, ¶15), and promoted (as did many other experts in the field of AIDS) the use of inactive Tat in humans to avoid the harmful effects that they believed would be caused by administration of biologically active HIV Tat to humans (see Third Ensoli Declaration, ¶16). The publications discussed in Paragraph Nos. 13-16 of the Third Ensoli Declaration are evidence of the clear skepticism and disbelief by experts in the art as to the safety of administering biologically active HIV Tat (or a biologically active HIV Tat mutant or fragment) to humans, and thus provide additional evidence of nonobviousness of the claimed invention. Evidence that experts expressed skepticism upon learning of the invention is also probative evidence of nonobviousness. *See United States v. Adams*, 383 U.S. at 52.

Applicant submits that the Third Ensoli Declaration is evidence that one of ordinary skill in the art as of December 1, 1997, faced with Chang *et al.* and the other references cited in support of the Section 103(a) rejections, would not have reason to modify the known procedures for obtaining a biologically active HIV Tat, which result in a composition that is not pharmaceutically acceptable for administration to humans, to obtain a biologically active HIV Tat (or biologically active HIV Tat mutant or fragment) in a composition that would be pharmaceutically acceptable for administration to a human. The Third Ensoli Declaration shows that it was unexpected that a composition comprising biologically active HIV (or a biologically active HIV Tat mutant or fragment) Tat would be beneficial and safe when administered to humans. The Third Ensoli Declaration evidences the clear skepticism and disbelief by experts existed in the art as to the safety of administering biologically active HIV Tat (or a biologically active HIV Tat mutant or fragment) to humans when the present invention was disclosed to them. Such unexpected results and skepticism by experts are secondary considerations of nonobviousness that must be considered in determining whether the claimed invention is obvious. *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467; see also Examination Guidelines, page 57527, paragraph bridging cols. 1-2. Applicant submits that such secondary considerations are sufficient both to rebut any *prima facie* case of obviousness made by the Examiner and to demonstrate the nonobviousness of the claimed invention. Accordingly, reconsideration and withdrawal of the Section 103(a) rejection are respectfully requested.

IV. FOREIGN PRIORITY CLAIM

The subject application No. 09/555,534 ("the '534 application") is a national stage of International Application No. PCT/EP98/07721 filed November 30, 1998, which claims priority to Italian Patent Application No. RM97A000743 filed December 1, 1997 ("the Priority Application"). Thus, the '534 application claims under 35 U.S.C. § 119(a) benefit of the Priority Application. A certified copy of the Priority Application was filed during the International Stage of PCT/EP98/07721, and the submission was acknowledged by the World Intellectual Property Organization (WIPO) (see face page of Exhibit A, a copy of the certified copy of the Priority Application, stamped received by WIPO on March 15, 1999).

On December 12, 2007, Applicant's representative Ann Chen telephoned Ms. Catherine Short at the Office of PCT Operations in the United States Patent and Trademark Office ("PTO") to confirm that a copy of the Priority Application had been received by the PTO, as indicated on the Notification of Acceptance of Application Under 35 U.S.C. 371 and 37 CFR 1.494 or 1.495 ("Notification") dated August 11, 2000. Ms. Short confirmed that said Notification, in particular, the check next to the "Priority Document" box, indicates the PTO's receipt of the Priority Application. Ms. Short, however, indicated that a copy of the certified copy of the Priority Application appeared to be missing from the PTO's imaged file for the '534 application, and indicated that she would obtain another copy of the Priority Application from WIPO. In view of her pending absence due to the holidays, Ms. Short suggested that, as an alternative, Applicant might wish to obtain a copy of the certified copy of the Priority Application directly from WIPO and provide the copy to the PTO. Applicant accordingly obtained such a copy, submitted herewith as Exhibit A.

Additionally, on January 15, 2008, Applicant's representative Ann Chen telephoned Ms. Shorts to follow up on whether the PTO had been able to obtain a copy of the certified copy of the Priority Application. In response, Ms. Shorts indicated that the PTO did submit a request to WIPO for a copy of the certified copy of the Priority Application, and suggested Applicant check the PTO Patent Application Information Retrieval (PAIR) website in a few days to confirm that the copy of the certified copy of the Priority Application had been imaged and made of record in the PTO's files.

On January 24, 2008, Applicant's representative Ann Chen checked the PTO Private PAIR website for the above-identified application No. 09/555,534, and noticed that a copy of the certified copy of the Priority Application had been uploaded and was now available under the Image File Wrapper. Thus, the PTO has received the certified copy of the Priority

Application, in connection with the present '534 application's claim to foreign priority. Accordingly, Applicant respectfully requests that the Examiner amend the Office Action Summary to reflect receipt of such certified copy of the Priority Application.

In addition, Applicant submits concurrently herewith as Exhibit B a copy of the certified English translation of the Priority Application. Applicant submits that the filing of the certified copy of the Priority Application during the international phase, which copy is now presented in the PTO's file for the application, and the English translation of the Priority Application submitted herewith perfect the foreign priority claim.

V. INFORMATION DISCLOSURE STATEMENT FILED ON NOVEMBER 17, 2000 AND RESUBMITTED ON BOTH DECEMBER 13, 2005 AND JUNE 14, 2006

It has come to the attention of Attorneys for Applicant that the replacement copy of the List of Related Art Cited By Applicant originally filed on November 17, 2000 and resubmitted on December 13, 2005, and resubmitted as a Replacement 1449 List of References Cited by Applicant ("List") on June 14, 2006, has not been initialed by the Examiner and returned to Applicant. A courtesy copy of the List is enclosed herewith as Exhibit C. It is respectfully requested that the List be initialed by the Examiner and returned to Applicant.

VI. THE WITHDRAWN CLAIM REJECTIONS UNDER 35 U.S.C. § 112

The Examiner has withdrawn the rejection of claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168, and 179-191 under 35 U.S.C. § 112, first paragraph. Specifically, in withdrawing the rejection, the Examiner states that "the Magnani declaration show[s] that it is common knowledge in the art to obtain a composition comprising a biologically active Tat that is pharmaceutically acceptable for administration to a human" (see page 4, ¶2, lines 5-6). Applicant respectfully disagrees with the Examiner's characterization of the First Magnani Declaration, and submits that the correct statement is that the First Magnani Declaration shows that one skilled in the art would be able to use common knowledge in the art to obtain such a composition without undue experimentation (once knowledge of the instant specification had motivated him/her to do so).

VII. DECLARATIONS BY BARBARA ENSOLI, M.D., Ph.D.

Applicant wishes to bring to the Examiner's attention the fact that Dr. Barbara Ensoli, who is the inventor of this application, also is an employee of the Istituto Istituto Superiore di Sanità, the Assignee of this application. Specifically, from 1996-1999, Dr. Ensoli was employed as the Director of Research, Laboratory of Virology, Istituto Superiore di Sanità. From 2000-2004, Dr. Ensoli was employed as the Director of the Retrovirus Division, Laboratory of Virology, Istituto Superiore di Sanità; and during 2004, Dr. Ensoli was employed as the Director of the AIDS Division, Department of Infectious, Parasitic and Immune-mediated Diseases, Istituto Superiore di Sanità. Dr. Ensoli has served as the Director of the National AIDS Center at the Istituto Superiore di Sanità since 2005.

VIII. DECLARATIONS BY SHAYNE GAD, Ph.D.

Applicant wishes to bring to the Examiner's attention the fact that Dr. Shayne Gad has been paid for his services rendered in connection with the prosecution of this application. In particular, Dr. Gad has been paid a consulting fee for his involvement in the preparation of the Declaration of Shayne Gad, Ph.D. Under 37 C.F.R. § 1.132, filed December 13, 2005, and the Second Declaration of Shayne Gad, Ph.D. Under 37 C.F.R. § 1.132, filed June 14, 2006.

CONCLUSION

Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: May 8, 2008

Adriane M. Antler 32,605
Adriane M. Antler (Reg. No.)

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Enclosures